

Breaking the wall of cancer immunotherapy with immunogenic cell death induction

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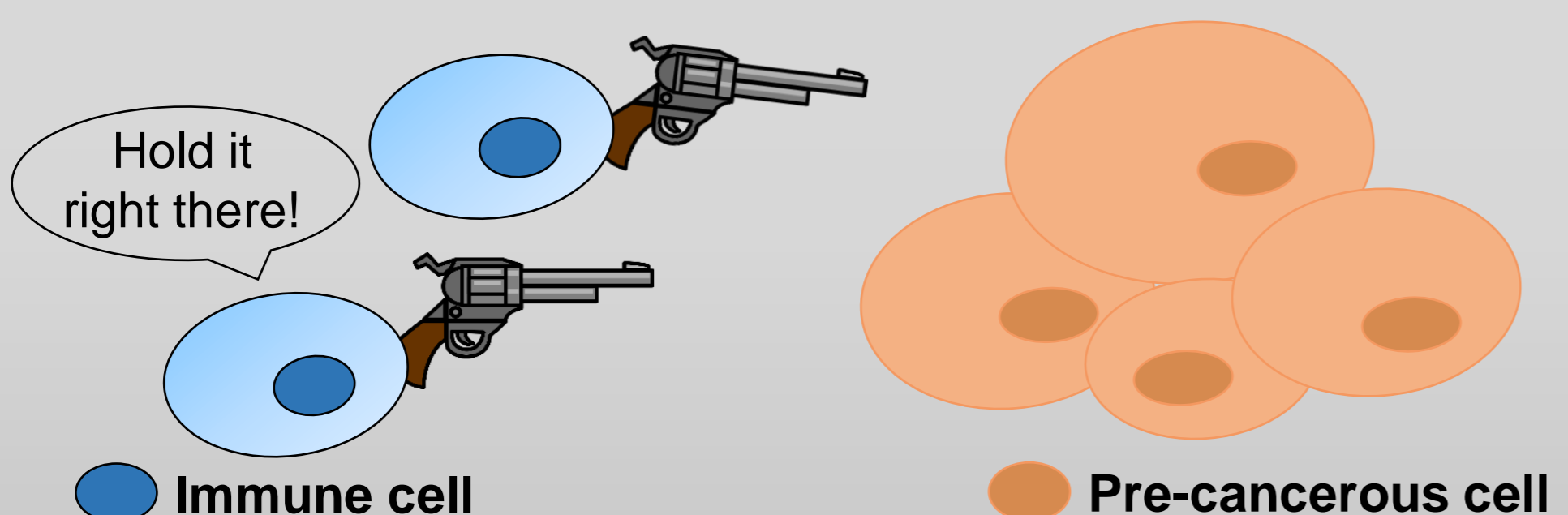
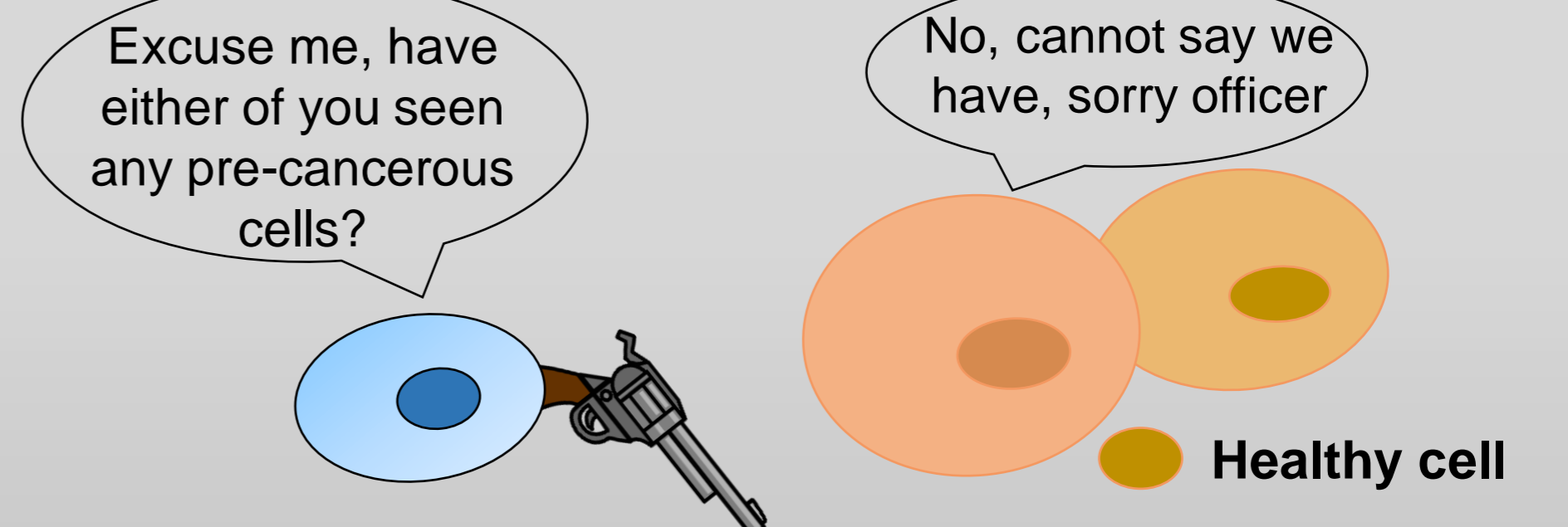
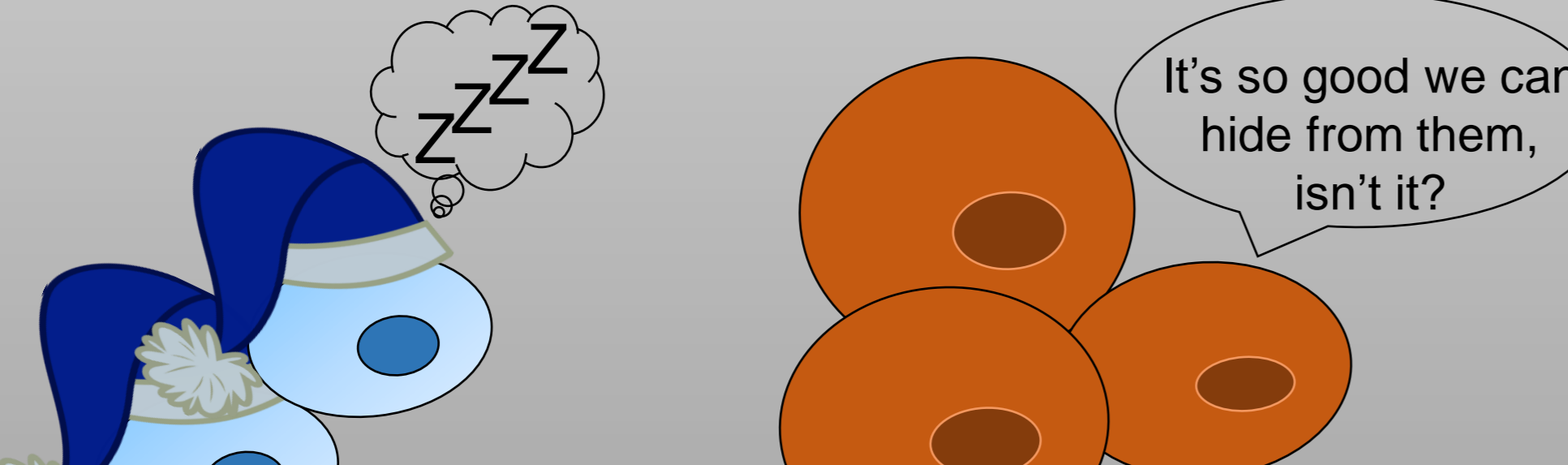
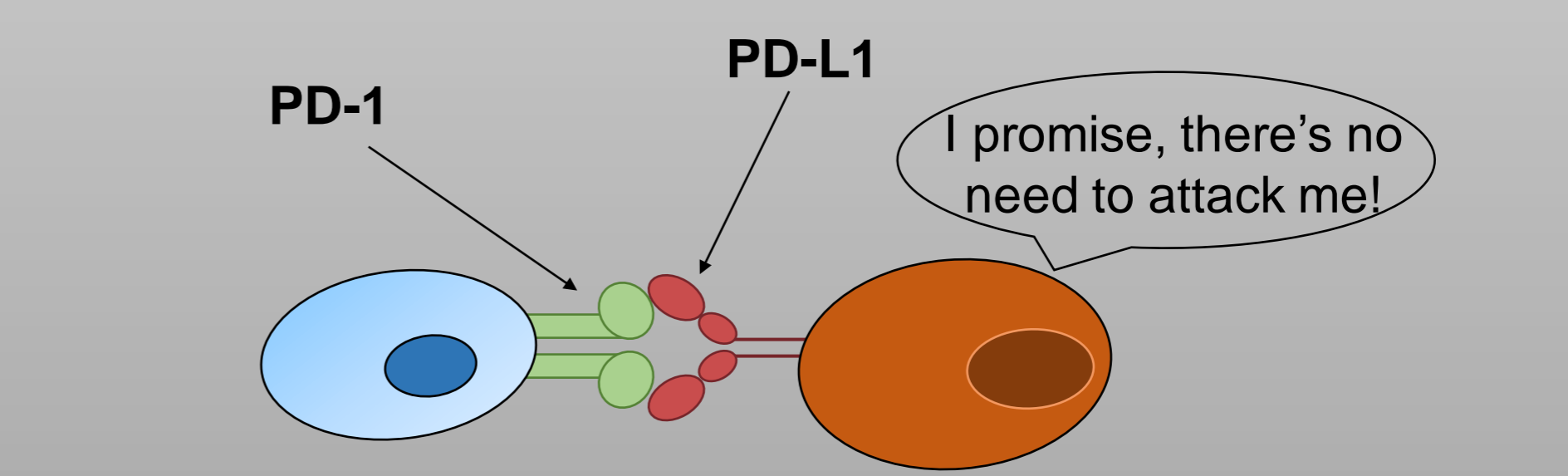
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Introduction


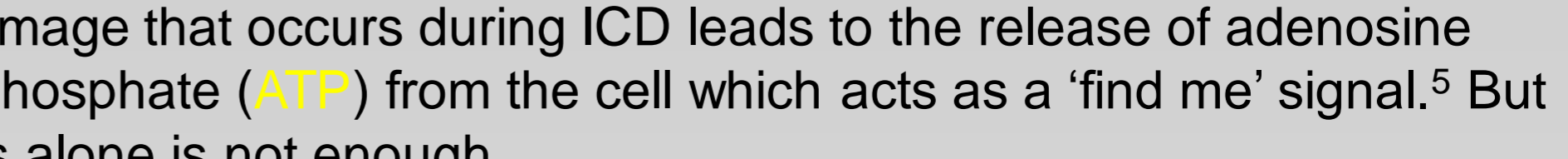
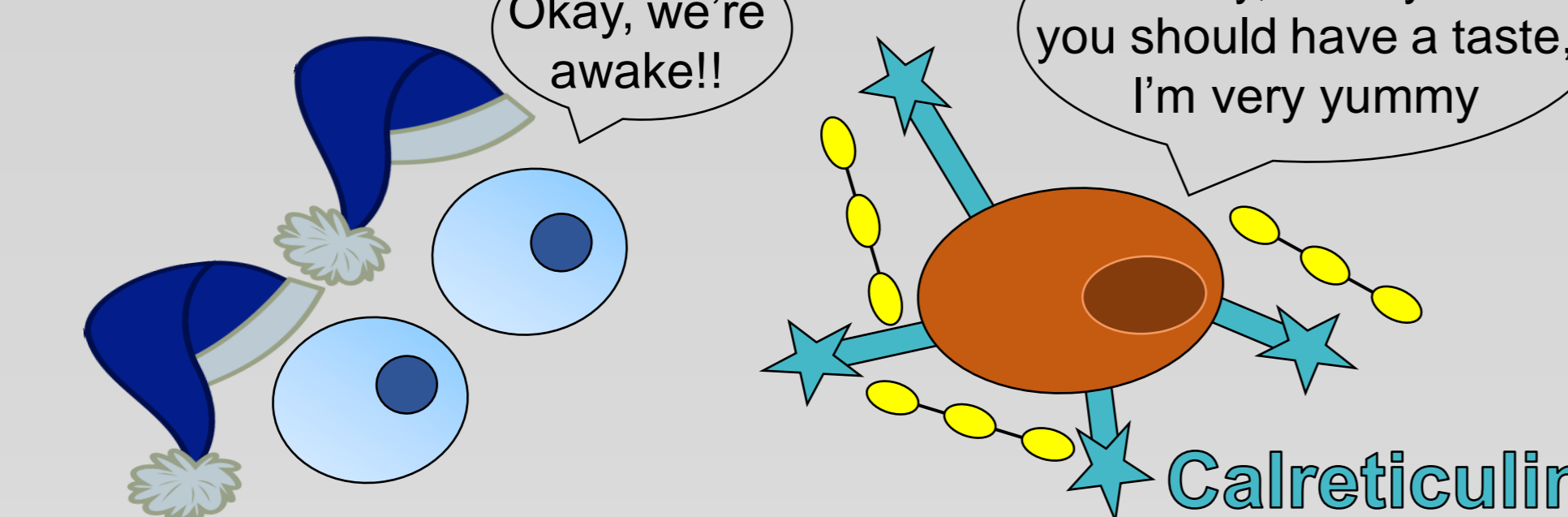
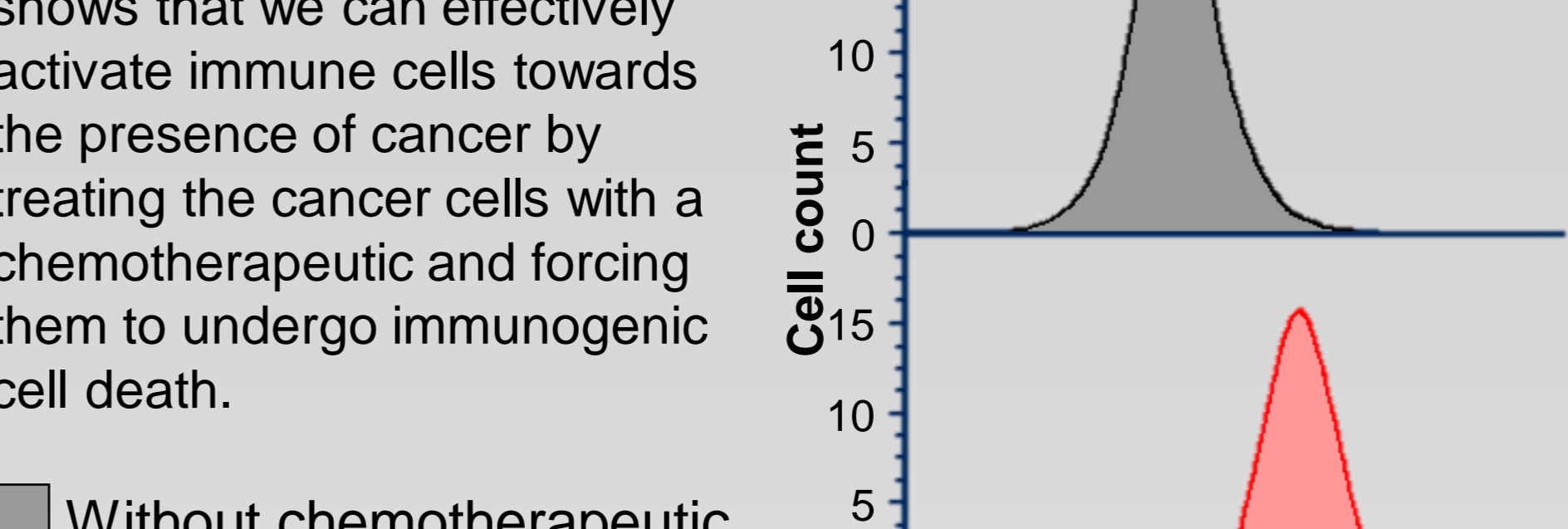
Cancer remains one of the leading causes of death in Aotearoa New Zealand, with disparities in 5-year survival rates across cancer types alarming.^{1,2} Melanoma, breast (female) and testicular cancer have 5-year survival rates of at least 80%.² Meanwhile, lung, liver and pancreatic cancer have 5-year survival rates of less than 15%.² These statistics paint two pictures. If you are diagnosed with one cancer type there is hope. Receive another diagnosis and you are hopeless. To provide a greater chance of survival for cancer patients we must continue to develop innovative modalities of treatment. Chemotherapeutics have been a mainstay in treatment for decades, and 21st century thinking is to explore their potential in immunotherapy.

The Immune System vs. Cancer

 <p>Hold it right there!</p> <p>● Immune cell</p> <p>● Pre-cancerous cell</p>	 <p>Excuse me, have either of you seen any pre-cancerous cells?</p> <p>No, cannot say we have, sorry officer</p> <p>● Healthy cell</p>
<p>To begin with, our immune cells are relatively good at identifying pre-cancerous cells and taking them out.³</p>	<p>However, as a cell acquires more mutations it becomes harder to tell a pre-cancerous cell apart from a healthy cell.³</p>
 <p>zzzz</p> <p>It's so good we can hide from them, isn't it?</p> <p>● Cancer cell</p>	 <p>PD-1</p> <p>PD-L1</p> <p>I promise, there's no need to attack me!</p>
<p>Until eventually our immune cells are oblivious to the fact that cancer cells are present in our body.³</p>	<p>On the off chance a cancer cell is recognised, it can stop an attack by sending inhibitory signals from its programmed death-ligand 1 (PD-L1) to the programmed death-1 (PD-1) protein found on immune cells.⁴</p>

The Project – Reawakening Immune Cells

Immunotherapies, such as the monoclonal antibody pembrolizumab, have been developed to overcome the PD-1/PD-L1 mechanism.⁵ However, objective response rates are low, with only 20-40% of patients receiving any therapeutic benefit.⁵ To drastically increase the number of patients that respond, we need to reawaken our immune cells. We can make a cancer cell do this job for us by treating it with a chemotherapeutic to induce a process known as immunogenic cell death (ICD).⁶

 <p>zzzz</p> <p>Okay, we're awake!!</p>	 <p>Hello, it's me here, a nasty cancer cell!</p> <p>ATP</p>
<p>Damage that occurs during ICD leads to the release of adenosine triphosphate (ATP) from the cell which acts as a 'find me' signal.⁵ But this alone is not enough</p>	<p>The histogram on the right shows that we can effectively activate immune cells towards the presence of cancer by treating the cancer cells with a chemotherapeutic and forcing them to undergo immunogenic cell death.</p>
 <p>Honestly, I really think you should have a taste, I'm very yummy</p> <p>● Calreticulin</p>	 <p>Cell count</p> <p>Immune cell activation</p> <p>Without chemotherapeutic</p> <p>With chemotherapeutic</p>
<p>Another hallmark ICD damage-associated pattern is the cell surface expression of calreticulin (CALR) which acts as an 'eat me' signal.⁵</p>	<p>20</p> <p>15</p> <p>10</p> <p>5</p> <p>0</p> <p>15</p> <p>10</p> <p>5</p> <p>0</p> <p>10¹ 10² 10³ 10⁴ 10⁵ 10⁶</p>

The Project Goals

- Investigate a library of anticancer agents and identify novel compounds which induce immunogenic cell death in a range of cancer cell types.
- Investigate the ability for cancer cells undergoing chemotherapy induced immunogenic cell death to initiate a robust immune response
- Synthetically optimise lead compounds to increase their viability as future clinical immunotherapy agents.

References

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